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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
O DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
04/24/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/574,972	DOI ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 23-33 are pending.

Request for Continued Examination

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 27, 2009 has been entered.

Response to Arguments and Remarks

3. Applicant's representatives arguments filed on February 27, 2009 have been fully considered but they are not persuasive, and the rejection of claims 23-33 under 103(a) is maintained. A new limitation was added for "inhibiting…..VEGF-A…." and is addressed below. The discovery of the way that a prior art method operates when the method steps are obvious, does not impart patentability. The overall invention of treating angiogenesis is obvious as demonstrated by the examiner, and any mechanistic discoveries do not take away from the obviousness of the actual method steps which do not change regardless of new descriptions of interactions that were not previously known. Several of the arguments of counsel have been addressed before and the previous discussion will not be repeated here, however the rejection is now made in view of in view of Bickwell et. al. *Tumour Angiogenesis* **1997**, Oxford Univ. pg. 19 AND Joyce Bischoff "Perspectives Series: Cell Adhesion in Vascular Biology Cell Adhesion and Angiogenesis" *Journal of Clinical Investigation* (99) 3, February **1997**, 373–376 AND Tei et. al. "Roles of Cell Adhesion Molecules in Tumor Angiogenesis Induced by Cotransplantation

of Cancer and Endothelial Cells to Nude Rats" CANCER RESEARCH 2002, 62, 6289–6296, which were brought out in the previous response to the traversal of the 103(a) rejection.

The affidavit under 37 CFR 1.132 filed February 27, 2009 is insufficient to overcome the rejection of claims 23-33 based upon a rejection under 103(a) as set forth in the last Office action because: The affidavit merely states what is already contained in the specification. The conclusion of the affiant that it would not have been obvious that the compounds of the instant claims inhibit VEGF-A based on the prior art is not relevant since the claims are drawn to a "method of inhibiting angiogenesis". The method step being the same such considerations are not needed. The discovery of the way that a prior art method operates when the method steps are obvious, does not impart patentability. The overall invention of treating angiogenesis is obvious as demonstrated by the examiner, and any mechanistic discoveries do not take away from the obviousness of the actual method steps which do not change regardless of new descriptions of interactions that were not previously known. The double patenting rejections are also maintained for these reasons.

A new rejection for solvate is now made.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 23-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over U. S. patent 6,498,169 (cited on the IDS) in view of Bickwell et. al. *Tumour Angiogenesis* **1997**, Oxford Univ. pg. 19 AND Joyce Bischoff "Perspectives Series: Cell Adhesion in Vascular Biology Cell Adhesion and Angiogenesis" *Journal of Clinical Investigation* (99) 3, February **1997**, 373–376 AND Tei et. al. "Roles of Cell Adhesion Molecules in Tumor Angiogenesis Induced by Cotransplantation of Cancer and Endothelial Cells to Nude Rats" CANCER RESEARCH 2002, 62, 6289–6296. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

A) Determining the scope and contents of the prior art.
B) Ascertaining the differences between the prior art and the claims at issue.
C) Resolving the level of ordinary skill in the pertinent art.
D) Considering objective evidence present in the application indicating obviousness or nonobviousness.

A) Determining the scope and contents of the prior art: The '169 patent teaches the elected species of the instant case, moreover the '169 patent also teaches that the elected species and other compounds of the instant case are inhibitors of endothelial cell adhesion (column 118 - 119, Table 1). Bickwell teaches that "alignment of endothelial cells into tube-like structures" or adhesion of these cells to one another, is a key step in angiogenesis. Moreover Bicknell teaches that angiogenesis is important for the growth of solid tumors.

B) Ascertaining the differences between the prior art and the claims at issue.

The process of the instant case involves the "inhibiting angiogenesis" and treating solid tumors with 4-[N-(4-methoxyphenyl)-N-[[5-(3,4,5-trimethoxyphenyl)pyridin-3-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl) pyridin-4-yl] methyl] piperidine, while the prior art teaches the

inhibition of cell adhesion with 4-[N-(4-methoxyphenyl)-N-[[5-(3,4,5-trimethoxyphenyl)pyridin-3-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl) pyridin-4-yl] methyl] piperidine. It goes without saying that the compounds and their method of administration is identical. It would appear then that the applicant seems to believe that a new property has been discovered.

C) Resolving the level of ordinary skill in the pertinent art: The level of ordinary skill is high. Someone using these compounds would be a medical doctor.

D) Considering objective evidence present in the application indicating obviousness or nonobviousness: One of ordinary skill would have realized based on the teachings of Bicknell et. al. that inhibitors of endothelial cell adhesion would also find use as angiogenesis inhibitors and for the treatment of solid tumors. It is well understood in the art that cell alignment and angiogenesis in general necessarily involve cell adhesion and the following reference is submitted to show that in fact when one is speaking of the alignment of endothelial cells and angiogenesis, adherence is necessarily taking place:

"Endothelial cell proliferation is a major component of angiogenesis, but is only one of a series of tasks the endothelial cells must accomplish to form a new capillary blood vessel. In response to angiogenic stimuli, endothelial cells degrade the extracellular matrix (ECM),[1] migrate into the perivascular space, proliferate, and align themselves into patent blood vessels. When sufficient angiogenesis has occurred, the endothelial cells become quiescent and the vessels either remain or regress if no longer needed. **During these events, the endothelial cells must adhere to one another** and to the ECM to construct and extend new microvessels." Joyce Bischoff "Perspectives Series: Cell Adhesion in Vascular Biology Cell Adhesion and Angiogenesis" *Journal of Clinical Investigation* (99) 3, February **1997**, 373–376. (pg. 373 paragraph 2)

Cell adhesion between leukocytes and endothelial cells alone can in fact be a requirement of angiogenesis as shown by the following citation:

"**However, angiogenesis sometimes depends on the interaction of endothelial cells with other types of cells**, and the roles of cell adhesion molecules in such interaction remain to be

studied. It is noteworthy that the in vitro angiogenesis of bovine aortic endothelial cells induced by polymorphonuclear leukocytes requires adhesion of leukocytes to endothelial cells through E-selectin and integrin/intercellular adhesion molecule-1 interaction (44, 45). When added to the coculture of F-2 cells with A431 cells, the anti-sialyl Lex/Lea antibodies as well as anti-β1-integrin antibody significantly inhibited the interaction of endothelial cells with cancer cells. The orderly formation of cancer cell nests surrounded by functional vascular networks of F-2 cells was almost completely inhibited by these antibodies both in vitro and in vivo. **Our results indicated that the interaction of cancer cells with endothelial cells through adhesion molecules such as selectins and integrins is critical for generation of functional vascular networks nourishing cancer cell nests and promoting in vivo growth of tumors.** The novel in vitro and in vivo model experimental systems described here offer a unique opportunity to study direct or indirect interaction between cancer cells and endothelial cells together with the outcome." Tei et. al. "Roles of Cell Adhesion Molecules in Tumor Angiogenesis Induced by Cotransplantation of Cancer and Endothelial Cells to Nude Rats" CANCER RESEARCH 2002, 62, 6289–6296.

The prior art '169 patent teaches that HUVECs stimulated with the cyctokine TNF-alpha become adherent to U937 cells and that the compounds of the instant invention block this adherence. The HUVECs are epithelial cells widely used in studies of angiogenesis. The U937 cells are lymphatic cancer cells. Clearly given the close connection between angiogenesis and cell adhesion, as shown above only one conclusion can be reached that invention as a whole is obvious over the prior art. A person of ordinary skill in the art would have been motivated to do so based on the desire to treat tumors which are not desirable tissues. The discovery of the way that a prior art method operates when the method steps are obvious, does not impart patentability. The overall invention of treating angiogenesis is suggested in the art, any mechanistic discoveries do not take away from the obviousness of the actual method steps which do not change regardless of new descriptions of interactions. Inhibition of VEGF-A is an inherent, inevitable result of the practice, and while not discovered in the prior art, discovery of details how an obvious process operates does not change the conclusion of obviousness.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 23-33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13-17 of U.S. Patent No. 6,395,753 in view of in view of Bickwell et. al. *Tumour Angiogenesis* **1997**, Oxford Univ. pg. 19 AND Joyce Bischoff "Perspectives Series: Cell Adhesion in Vascular Biology Cell Adhesion and Angiogenesis" *Journal of Clinical Investigation* (99) 3, February **1997**, 373–376 AND Tei et. al. "Roles of Cell Adhesion Molecules in Tumor Angiogenesis Induced by Cotransplantation of Cancer and Endothelial Cells to Nude Rats" CANCER RESEARCH 2002, 62, 6289–6296. Although the conflicting claims are not identical, they are not patentably distinct from each other because the current claims although drawn to "inhibiting angiogenesis" and methods of treating diseases caused by angiogenesis the '753 patent, covers methods of treating diseases caused by cell adhesion with the same compounds. See the 103(a) rejection above for a detailed discussion.

6. Claims 23-33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 15-20 of U.S. Patent No. 6,498,169 in view of in view of Bickwell et. al. *Tumour Angiogenesis* **1997**, Oxford Univ. pg. 19 AND Joyce Bischoff "Perspectives Series: Cell Adhesion in Vascular Biology Cell Adhesion and Angiogenesis" *Journal of Clinical Investigation* (99) 3, February **1997**, 373–376 AND Tei et. al. "Roles of Cell Adhesion Molecules in Tumor Angiogenesis Induced by Cotransplantation of Cancer and Endothelial Cells to Nude Rats" CANCER RESEARCH 2002, 62, 6289–6296. Although the conflicting claims are not identical, they are not patentably distinct from each other because the current claims although drawn to "inhibiting angiogenesis" and methods of treating diseases caused by angiogenesis the '169 patent, covers methods of treating diseases caused by cell adhesion with the same compounds. See the 103(a) rejection above for a detailed discussion.

7. Claims 23-33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 3 of U.S. Patent No. 6,605,620, in view of Bickwell et. al. *Tumour Angiogenesis* **1997**, Oxford Univ. pg. 19 AND Joyce Bischoff "Perspectives Series: Cell Adhesion in Vascular Biology Cell Adhesion and Angiogenesis" *Journal of Clinical Investigation* (99) 3, February **1997**, 373–376 AND Tei et. al. "Roles of Cell Adhesion Molecules in Tumor Angiogenesis Induced by Cotransplantation of Cancer and Endothelial Cells to Nude Rats" CANCER RESEARCH 2002, 62, 6289–6296. Although the conflicting claims are not identical, they are not patentably distinct from each other because the current claims although drawn to "inhibiting angiogenesis" and methods of treating diseases caused by angiogenesis the '620 patent, covers methods of treating diseases caused by cell adhesion with the same compounds. See the 103(a) rejection above for a detailed discussion.

8. Claims 23-33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13-17 of U.S. Patent No. 6,867,221 in view of in view of Bickwell et. al. *Tumour Angiogenesis* **1997**, Oxford Univ. pg. 19 AND Joyce Bischoff "Perspectives Series: Cell Adhesion in Vascular Biology Cell Adhesion and Angiogenesis" *Journal of Clinical Investigation* (99) 3, February **1997**, 373–376 AND Tei et. al. "Roles of Cell Adhesion Molecules in Tumor Angiogenesis Induced by Cotransplantation of Cancer and Endothelial Cells to Nude Rats" CANCER RESEARCH 2002, 62, 6289–6296. Although the conflicting claims are not identical, they are not patentably distinct from each other because the current claims although drawn to "inhibiting angiogenesis" and methods of treating diseases caused by angiogenesis the '221 patent, covers methods of treating diseases caused by cell adhesion with the same compounds. See the 103(a) rejection above for a detailed discussion.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 23-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making solvates of the claimed compounds. The specification does not enable any person skilled in the art of synthetic organic chemistry to make the invention commensurate in scope with these claims. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of

the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. In the present case the important factors leading to a conclusion of undue experimentation are the absence of any working example of a formed solvate, the lack of predictability in the art, and the broad scope of the claims.

a) Determining if any particular substrate would form a solvate or hydrate would require synthesis of the substrate and subjecting it to recrystallization with a variety of solvents, temperatures, pressures, and humidity. The experimentation is potentially open-ended. b) The direction concerning the hydrates is not found in the specification. c) There is no working example of any hydrate or solvate formed. The claims are drawn to solvates, yet the numerous examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

d) The nature of the invention is chemical synthesis, which involves chemical reactions. e) g) Chemical reactions are well-known to be unpredictable, *In re Marzocchi*, 169 USPQ 367,

In re Fisher, 166 USPQ 18. The state of the solvate art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). West, Anthony R., "Solid State Chemistry and its Applications, Wiley, New York, 1988, pages 358 & 365. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. In the same paragraph on page 365 West (Solid State Chemistry) explains that it is possible to make meta-stable non-equilibrium solvates, further clouding what Applicants mean by the word solvate. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the solvate. h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula IIa as well as the presently unknown list of solvents embraced by the term "solvate". Thus, the scope is broad.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27

USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Conclusion

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

/Rita J. Desai/
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